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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
LU, FRANK WEI MIN

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 02/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/829,066	NISSON ET AL.	
	Examiner	Art Unit	
	Frank W Lu	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 December 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6-8,41,72 and 73* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6-8,41,72 and 73* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Examination

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on December 1, 2003 has been entered. The claims pending in this application are claims 1-4, 6-8, 41, 72, and 73. Rejection and/or objection not reiterated from the previous office action are hereby withdrawn in view of applicant's amendment filed on December 1, 2003.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1-4, 6-8, 41, 72, and 73 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

4. Claims 1 and 73 are rejected as vague and indefinite because it is unclear whether "one or more nucleic acid molecules" in step ii) of the claims are identical to "one or more double stranded nucleic acids" in step i) of the claims or not. Please clarify.

5. Claim 72 is rejected as vague and indefinite because it is unclear that said one or more nucleic acid molecules recited in claim 72 is said one or more double stranded

nucleic acid molecules or said one or more single stranded nucleic acid molecules as recited in claim 1. Note that claim 1 has double stranded nucleic acid molecules and single stranded nucleic acid molecules. Please clarify.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 1, 2, 4, 6, and 41 are rejected under 35 U.S.C. 102(b) as being anticipated by Allison *et al.*, (US Patent No. 5,650,167, published on July 22, 1997) as evidence by Inman *et al.*, (J. Mol. Biol., 49, 93-98, 1970).

Allison *et al.*, teach method and composition for treating hepatitis B.

Regarding claims 1, 2, 4, and 41, Allison *et al.*, teach to denature viral nucleic acids in a supernatant fluid from monolayer culture in 96 well plates with 1 M NaOH and then load neutralized viral nucleic acids in the supernatant fluid to a nylon membrane. The viral nucleic acids on the membrane are crosslinked to the membrane by UV light and hybridized with HBV DNA in the presence of Denhardt's solution containing 1% glycine (see column 11, last paragraph and column 12, first paragraph). Since it is known that NaOH only partially denatures a double stranded DNA (see Inman *et al.*, abstract in page 93, fifth paragraph in page 94, and first paragraph in page 97), the viral nucleic acids on the membrane taught by Allison *et al.*, contain both single stranded and double stranded viral nucleic acids. According to claim 4 of this instant application, glycine is an

amino acid denaturant that has an ability to denature a double stranded nucleic acid to a single stranded nucleic acid. Since Allison *et al.*, teach to hybridize the viral nucleic acids on the membrane (containing double stranded nucleic acids) with the HBV DNA in the presence of Denhardt's solution containing 1% glycine, Allison *et al.*, disclose contacting one or more double-stranded nucleic acid molecules (ie., the viral nucleic acids containing double stranded nucleic acids on the membrane) with an amino acid denaturant (ie., glycine) thereby forming one or more single-stranded nucleic acid molecules (ie., single stranded viral nucleic acids in the membrane and in the Denhardt's solution) and combining said one or more single-stranded nucleic acid molecules with one or more nucleic acid molecules wherein said one or more nucleic acid molecules (ie., the HBV DNA) are capable of hybridizing to said single-stranded nucleic acid molecules thereby obtaining one or more of said hybridized nucleic acid molecules as recited in claim 1. Since Allison *et al.*, teach glycine and it is known that glycine is a natural amino acid or an amino acid denaturant, claims 2, 4, and 41 are anticipated by Allison *et al.*.

Regarding claim 6, since 1% glycine is equal to a concentration of about 135 mM glycine, claim 6 is anticipated by Allison *et al.*.

Therefore, Allison *et al.*, teach all limitations recited in claims 1, 2, 4, 6, and 41.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 1-2, 4, 6-8, and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zarling *et al.*, (US Patent No. 5,719,023, 102 (e) date: June 3, 1994) in view of Aslanyan *et al.*, (Biophysics, 29, 615-620, 1984).

Zarling *et al.*, teach in situ hybridization method.

Regarding claim 1, as shown in Examples 2 and 3, since Zarling *et al.*, teach that a double stranded chromosome X alpha satellite DNA probe is heat denatured to become a single stranded before in situ hybridization. During the hybridization, a single stranded chromosome X alpha satellite DNA probe is hybridized with target nucleic acids in Hep-2 cell nuclei that immobilized in slides (see columns 17 and 18), Zarling *et al.*, disclose contacting one or more double-stranded nucleic acid molecules (ie., a double stranded chromosome X alpha satellite DNA probe) with a denaturant (ie., the heat) thereby forming one or more single-stranded nucleic acid molecules (ie., a single stranded chromosome X alpha satellite DNA probe) and combining said one or more single-stranded nucleic acid molecules with one or more nucleic acid molecules wherein said

one or more nucleic acid molecules (ie., the target nucleic acids in Hep-2 cell nuclei that immobilized in slides) are capable of hybridizing to said single-stranded nucleic acid molecules thereby obtaining one or more of said hybridized nucleic acid molecules as recited in claim 1.

Zarling *et al.*, do not disclose to denature double stranded nucleic acid molecules using an amino acid denaturant as recited in i) of claim 1 and claims 2, 4, 6-8, and 41.

Regarding claims 1, 2, 4, 6-8, and 41, Aslanyan *et al.*, teach the effect of glycine on conformation and thermal stability of DNA. Since the intermolecular interaction between DNA and glycine causes sharp fall in the enthalpy of the helix-coil transition and leads to uncoiling of the DNA double helix (causing double stranded DNA to become single stranded) (see abstract in page 615, pages 616 and 617) and it is known that glycine is a natural amino acid, glycine is an amino acid denaturant as recited in claims 1, 2, 4, and 41. Since Aslanyan *et al.*, teach that glycine concentration with range of 1 mM- 3000 mM (log10 M =1 M =1000 mM, see Figure 1) reduces the melting point of calf thymus DNA (see Figures 1 and 2) and it is known that log 0.01 (M) (10 mM) equal to –2 (see Figure 1), claims 6-8 are anticipated by Aslanyan *et al.*.

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed a hybridization assay using a single stranded nucleic acid probe denatured by an amino acid denaturant in view of the prior art of Zarling *et al.*, and Aslanyan *et al.*. One having ordinary skill in the art would have been motivated to do so because Aslanyan *et al.*., have successfully used an amino acid denaturant (ie., glycine) to denature a double stranded nucleic acid probe into a single stranded nucleic acid probe and the simple replacement of one well known

denaturation method (i.e., heat denaturation taught by Zarling *et al.*,) from another well known denaturation method (i.e., denaturation by an amino acid denaturant taught by Aslanyan *et al..*,) during the process of a hybridization assay would have been, in the absence of convincing evidence to the contrary, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made because heat denaturation taught by Zarling *et al.*, and denaturation by an amino acid denaturant taught by Aslanyan *et al..*, are functional equivalent methods which are used for the same purpose.

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.06.

Response to Arguments

In page 10, second paragraph bridging to page 11, first paragraph of applicant's remarks, applicant argues that: (1) "there is no suggestion or motivation in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify Zarling et al. or to combine Zarling et al. with Aslanyan et al. to arrive at the claimed methodology."; and (2) "[A]bsent the teachings in Applicants' specification, the skilled artisan would not regard the denaturation methodology of Aslanyan et al. as a substitute or useful in the hybridization methodology discussed by Zarling et al. Applicants respectfully assert that the Examiner has improperly relied upon hindsight reasoning".

These arguments have been fully considered but they are not persuasive toward the withdrawal of the rejection. First, in response to applicant's argument that there is no

suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, since the knowledge of amino acid denaturants and a hybridization assay is generally available to one of ordinary skill in the art and combination of Zarling *et al.*, and Aslanyan *et al.*, teach all limitations recited in claims 1-4, 6-8, and 41, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed a hybridization assay using a single stranded nucleic acid probe denatured by an amino acid denaturant in view of the prior art of Zarling *et al.*, and Aslanyan *et al.*. because Aslanyan *et al..*, have successfully used an amino acid denaturant (ie., glycine) to denature a double stranded nucleic acid probe into a single stranded nucleic acid probe and the simple replacement of one well known denaturation method (i.e., heat denaturation taught by Zarling *et al.*,) from another well known denaturation method (i.e., denaturation by an amino acid denaturant taught by Aslanyan *et al..*,) during the process of a hybridization assay would have been, in the absence of convincing evidence to the contrary, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made because heat denaturation taught by Zarling *et al.*, and denaturation by an amino acid denaturant taught by Aslanyan *et al..*, are functional equivalent methods which are used for the same purpose (see MPEP 2144.06).

Second, in response to applicant's argument that the examiner's conclusion of

obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

10. Claims 1-3 and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zarling et al., (June 3, 1994) in view of Yoshida (Biochem. Biophys. Res. Commun., 116, 217-221, 1983).

The teachings of Zarling et al., have been summarized previously, *supra.*

Zarling et al., do not disclose to denature double stranded nucleic acid molecules using an amino acid denaturant comprising polyamino acids as recited in claims 1-3 and 41.

Regarding claims 1-3 and 41, Yoshida teaches Mg^{2+}, Ca^{2+}-dependent unwinding of DNA by poly-L-glutamic acid. Since the decrease of Tm of a double stranded DNA by poly-L-glutamic acid in the presence of Mg^{2+} or Ca^{2+} is due to the unwinding of DNA double-helix by poly-L-glutamic acid (see Figures 2-4 and first paragraph in page 220) and it is known that poly-L-glutamic acid is an unnatural amino acid, poly-L-glutamic acid is considered as an amino acid denaturant comprising a polyamino acids with two or more amino acids as recited in claims 1-3 and an unnatural amino acid as recited in claim 41.

Therefore, it would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to have performed a hybridization assay using a single stranded nucleic acid probe denatured by an amino acid denaturant comprising polyamino acids in view of the prior art of Zarling et al., and Yoshida. One having ordinary skill in the art would have been motivated to do so because Yoshida has successfully used an amino acid denaturant (ie., poly-L-glutamic acid) to denature a double stranded nucleic acid probe into a single stranded nucleic acid probe and the simple replacement of one well known denaturation method (i.e., heat denaturation taught by Zarling et al.,) from another well known denaturation method (i.e., denaturation by an amino acid denaturant taught by Yoshida) during the process of a hybridization assay would have been, in the absence of convincing evidence to the contrary, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made because heat denaturation taught by Zarling *et al.*, and denaturation by an amino acid denaturant taught by Yoshida are functional equivalent methods which are used for the same purpose.

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.06.

Response to Arguments

In page 12, first paragraph bridging to page 13, second paragraph of applicant's remarks, applicant argues that: (1) "there is no suggestion or motivation in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to

modify Zarling et al. or to combine Zarling et al. with Yoshida to arrive at the claimed methodology."; and (2) "[A]bsent the teachings in Applicants' specification, the skilled artisan would not regard the denaturation methodology of Yoshida as a substitute or useful in the hybridization methodology discussed by Zarling et al. Applicants respectfully assert that the Examiner has improperly relied upon hindsight reasoning".

These arguments have been fully considered but they are not persuasive toward the withdrawal of the rejection. First, in response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, since the knowledge of amino acid denaturants and a hybridization assay is generally available to one of ordinary skill in the art and combination of Zarling *et al.*, and Yoshida teach all limitations recited in claims 1-4, 6-8, and 41, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed a hybridization assay using a single stranded nucleic acid probe denatured by an amino acid denaturant in view of the prior art of Zarling *et al.*, and Yoshida because Yoshida has successfully used an amino acid denaturant (ie., poly-L-glutamic acid) to denature a double stranded nucleic acid probe into a single stranded nucleic acid probe and the simple replacement of one well known denaturation method (i.e., heat denaturation taught by Zarling et al.,) from another well known denaturation

method (i.e., denaturation by an amino acid denaturant taught by Yoshida) during the process of a hybridization assay would have been, in the absence of convincing evidence to the contrary, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made because heat denaturation taught by Zarling *et al.*, and denaturation by an amino acid denaturant taught by Yoshida are functional equivalent methods which are used for the same purpose (see MPEP 2144.06). Second, in response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

11. Claims 6-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zarling et al., (June 3, 1994) in view of Yoshida (1983) as applied to claims 1-3 above.

The teachings of Zarling et al., and Yoshida have been summarized previously, *supra.*

Zarling et al., and Yoshida do not disclose to use a concentration of amino acid denaturant as recited in claims 6-8. However, Yoshida shows integral thermal denaturation profiles of a double stranded DNA in the presence of different weight ratios of added poly-L-glutamic acid to the double stranded DNA such as 0.5 (see Figure 3). Since thermal melting transition of a double stranded DNA in a sample solution is

measured in a 4 ml cell by a Beckman Acta CIII spectrophotometer and molecular weight of poly-L-glutamic acid is 8,800 (see page 218, fourth paragraph), when the weight ratio of added poly-L-glutamic acid to the double stranded DNA is 0.5 and the double stranded DNA is 300 μg in the sample solution, the concentration of the added poly-L-glutamic acid is 4.26 μM (150 μg in 4 ml of the sample solution).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have used an amino acid denaturant with different concentrations in the method as recited in claim 1 in view of prior art of Zarling et al., and Yoshida. One having ordinary skill in the art has been motivated to do so because optimization of concentration of an amino acid denaturant during the process of denaturing a double stranded nucleic acid would have been, in the absence of convincing evidence to the contrary, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made. One having ordinary skill in the art at the time the invention was made would have been a reasonable expectation of success to optimize concentration of an amino acid denaturant during the process of denaturing a double stranded nucleic acid. Note that, where the general conditions of a claim are disclosed in the prior art, it is not inventive, in the absence of an unexpected result, to discover the optimum or workable ranges by routine experimentation. In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) (see MPEP 2144.05).

Response to Arguments

In page 13, last paragraph bridging to page 14, third paragraph of applicant's remarks, applicant argues that: (1) "there is no suggestion or motivation in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to

modify Zarling et al. or to combine Zarling et al. with Yoshida to arrive at the claimed methodology."; and (2) "a *prima facie* case of obviousness has not been made because neither the references alone or in combination teach or suggest all the claim limitations" since the concentration of amino acid denaturant used by Yoshida is "*three orders of magnitude* outside of the claimed ranges.".

These arguments have been fully considered but they are not persuasive toward the withdrawal of the rejection. First, in response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, since the knowledge of amino acid denaturants and a hybridization assay is generally available to one of ordinary skill in the art and combination of Zarling *et al.*, and Yoshida teach all limitations recited in claims 1-4, 6-8, and 41, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed a hybridization assay using a single stranded nucleic acid probe denatured by an amino acid denaturant in view of the prior art of Zarling *et al.*, and Yoshida because Yoshida has successfully used an amino acid denaturant (ie., poly-L-glutamic acid) to denature a double stranded nucleic acid probe into a single stranded nucleic acid probes and the simple replacement of one well known denaturation method (i.e., heat denaturation taught by Zarling *et al.*,) from another well known denaturation method (i.e., denaturation by an

amino acid denaturant taught by Yoshida) during the process of a hybridization assay would have been, in the absence of convincing evidence to the contrary, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made because heat denaturation taught by Zarling *et al.*, and denaturation by an amino acid denaturant taught by Yoshida are functional equivalent methods which are used for the same purpose (see MPEP 2144.06). Second, although the concentration of amino acid denaturant used by Yoshida is "*three orders of magnitude* outside of the claimed ranges.", it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have used an amino acid denaturant with different concentrations in the method as recited in claim 1 in view of prior art of Zarling *et al.*, and Yoshida because optimization of concentration of an amino acid denaturant during the process of denaturing a double stranded nucleic acid would have been, in the absence of convincing evidence to the contrary, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made. One having ordinary skill in the art at the time the invention was made would have been a reasonable expectation of success to optimize concentration of an amino acid denaturant during the process of denaturing a double stranded nucleic acid. Note that, where the general conditions of a claim are disclosed in the prior art, it is not inventive, in the absence of an unexpected result, to discover the optimum or workable ranges by routine experimentation. In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) (support from MPEP 2144.05).

12. Claims 7 an 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Allison *et al.*, (1997) as evidence by Inman *et al.*, (1970) as applied to claims 1, 2, 4, 6, and 41 above.

The teachings of Allison *et al.*, and Inman *et al.*, have been summarized previously, *supra.*

Allison *et al.*, and Inman *et al.*, do not disclose to use a concentration of amino acid denaturant as recited in claims 7 and 8 although Allison *et al.*, teach to use 1% glycine (a concentration of 135 mM glycine) (see above rejection under 35 USC 102).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have used an amino acid denaturant with different concentrations in the method as recited in claim 1 in view of prior art of Allison *et al.,* as evidence by Inman *et al.*. One having ordinary skill in the art has been motivated to do so because optimization of concentration of an amino acid denaturant during the process of denaturing a double stranded nucleic acid would have been, in the absence of convincing evidence to the contrary, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made. One having ordinary skill in the art at the time the invention was made would have been a reasonable expectation of success to optimize concentration of an amino acid denaturant during the process of denaturing a double stranded nucleic acid. Note that, where the general conditions of a claim are disclosed in the prior art, it is not inventive, in the absence of an unexpected result, to discover the optimum or workable ranges by routine experimentation. In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) (see MPEP 2144.05).

12. Claims 1, 2, 4, 6-8, 41, 72, and 73 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mitchell *et al.*, (Anal. Biochemistry, 178, 239-242, 1989) in view of Aslanyan *et al.*, (Biophysics, 29, 615-620, 1984).

Mitchell *et al.*, teach affinity generation of single-stranded DNA for dideoxy sequencing following the polymerase chain reaction. A polymerase chain reaction is performed in the presence of biotin-labeled primer. After amplification, the mixture containing a PCR product is passed through a column containing streptavidin agarose. The strand produced by the biotinylated primer on the PCR product is bound in this matrix. The unbiotinylated strand of the PCR product is eluted with 0.2 N NaOH and sequenced by the dideoxy method (see page 239, abstract).

Regarding claim 1, since Mitchell *et al.*, teach that the unbiotinylated strand of the PCR product is eluted with 0.2 N NaOH and it is known that PCR product is a double stranded DNA, Mitchell *et al.*, disclose contacting one or more double-stranded nucleic acid molecules (ie., the PCR product) with a denaturant (ie., 0.2 N NaOH) thereby forming one or more single-stranded nucleic acid molecules (ie., the unbiotinylated strand of the PCR product) as recited in i) of the claim. Since Mitchell *et al.*, teach to sequence the unbiotinylated strand of the PCR product using the dideoxy method and it is known that a sequencing reaction must include to anneal a template (ie., the unbiotinylated strand of the PCR product) with a sequencing primer and form a complex comprising the template and the sequencing primer, Mitchell *et al.*, disclose combining said one or more single-stranded nucleic acid molecules (ie., the unbiotinylated strand of the PCR product) with one or more nucleic acid molecules (ie., a sequencing primer) wherein said one or more nucleic acid molecules are capable of hybridizing to said

single-stranded nucleic acid molecules thereby obtaining one or more of said hybridized nucleic acid molecules as recited in ii) of the claim.

Regarding claim 72, since it is known that biotin is a common used hapten that can be detected by using it's strong affinity for the proteins avidin or streptavidin (see attachment), the biotin-labeled PCR product taught by Mitchell *et al.*, is a double stranded haptenylated nucleic acid molecule as recited claim 72.

Regarding claim 73, since Mitchell *et al.*, teach that, after amplification, the mixture containing a PCR product is passed through a column containing streptavidin agarose and the unbiotinylated strand of the PCR product is eluted with 0.2 N NaOH, and it is known that PCR product is a double stranded DNA and biotin is a common used hapten that can be detected by using it's strong affinity for the proteins avidin or streptavidin (see attachment), Mitchell *et al.*, disclose contacting one or more double-stranded nucleic acid molecules (ie., the PCR product) with a denaturant (ie., 0.2 N NaOH) thereby forming one or more non-haptenylated single-stranded nucleic acid molecules (ie., the unbiotinylated strand of the PCR product) and one or more haptenylated single-stranded nucleic acid molecules (ie., the biotinylated strand of the PCR product on the streptavidin agarose) as recited in i) of the claim. Since Mitchell *et al.*, teach to sequence the unbiotinylated strand of the PCR product using the dideoxy method and it is known that a sequencing reaction must include to anneal a template (ie., the unbiotinylated strand of the PCR product) with a sequencing primer and form a complex comprising the template and the sequencing primer, Mitchell *et al.*, disclose combining said one or more non-haptenylated single-stranded nucleic acid molecules (ie., the unbiotinylated strand of the PCR product) with one or more nucleic acid molecules

(ie., a sequencing primer) wherein said one or more nucleic acid molecules are capable of hybridizing to said single-stranded nucleic acid molecules thereby obtaining one or more of said hybridized nucleic acid molecules as recited in ii) of the claim.

Mitchell *et al.*, do not disclose that a denaturant selected from the group consisting of one or more amino acid denaturants as recited in claims 1 and 73.

Regarding claims 1, 2, 4, 6-8, and 41, Aslanyan *et al.*, teach the effect of glycine on conformation and thermal stability of DNA. Since the intermolecular interaction between DNA and glycine causes sharp fall in the enthalpy of the helix-coil transition and leads to uncoiling of the DNA double helix (causing double stranded DNA to become single stranded) (see abstract in page 615, pages 616 and 617) and it is known that glycine is a natural amino acid, glycine is an amino acid denaturant as recited in claims 1, 2, 4, and 41. Since Aslanyan *et al.*, teach that glycine concentration with range of 1 mM- 3000 mM (log10 M =1 M =1000 mM, see Figure 1) reduces the melting point of calf thymus DNA (see Figures 1 and 2) and it is known that log 0.01 (M) (10 mM) equal to –2 (see Figure 1), claims 6-8 are anticipated by Aslanyan *et al.*.

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed a hybridization assay recited in claims 1 and 73 using a non-haptenylated single stranded nucleic acid probe denatured by an amino acid denaturant in view of the prior art of Mitchell *et al.*, and Aslanyan *et al.*. One having ordinary skill in the art would have been motivated to do so because Aslanyan *et al.*., have successfully used an amino acid denaturant (ie., glycine) to denature a double stranded nucleic acid probe into a single stranded nucleic acid probe and the simple replacement of one well known denaturation method (i.e., NaOH

denaturation taught by Mitchell *et al.,*) from another well known denaturation method (i.e., denaturation by an amino acid denaturant taught by Aslanyan *et al..,*) during the process of a hybridization assay would have been, in the absence of convincing evidence to the contrary, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made because NaOH denaturation taught by Mitchell *et al.,* and denaturation by an amino acid denaturant taught by Aslanyan *et al..,* are functional equivalent methods which are used for the same purpose.

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.06.

Double Patenting

13. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

14. Claims 1-4, 6-8, 41, and 72 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-10 of U. S. Patent No. 6,268,133 in view of Zarling *et al.,* (June 3, 1994).

Although claims 1-4, 6-8, 41, and 72 in this instant application are much broader than claims 1-10 of U.S. Patent No.6,268,133 and have an additional step ii), claims 1-10 of U.S. Patent No.6,268,133 fall entirely within the scope of step i) of claim 1 and claims 2-9 of U.S. Patent No.6,268,133 are identical to claims 2-4, 6-8, and 41 of this instant application. Claim 10 of U.S. Patent No.6,268,133 discloses a haptenylated double stranded nucleic acid probe as recited in claim 72.

The teachings of Zarling *et al.,* have been summarized previously, supra. Zarling *et al.,* teaches step ii) of claim 1 (see above).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed a hybridization assay using a single stranded nucleic acid probe denatured by an amino acid denaturant in view of U.S. Patent No.6,268,133 and the prior art of Zarling *et al.*. One having ordinary skill in the art would have been motivated to do so because Zarling *et al.,* has successfully used a single stranded nucleic acid probe produced by denaturation for a hybridization assay and use of a single stranded nucleic acid for different assays such as a hybridization assay would have been, in the absence of convincing evidence to the contrary, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made. One having ordinary skill in the art at the time the invention was made would have been a reasonable expectation of success to use a single stranded nucleic acid probe denatured by an amino acid denaturant for a hybridization assay.

Response to Arguments

In page 14, last paragraph bridging to page 15, first paragraph of applicant's remarks, applicant argues that "[A]pplicants respectfully traverse and request reconsideration and withdrawal of the Double Patenting Rejection.".

This argument has been fully considered but it is not persuasive toward the withdrawal of the rejection because applicant does not explain why he traverses the examiner's double patenting rejection.

Conclusion

15. No claim is allowed.

16. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CAR § 1.6(d)). The CM Fax Center number is either (703) 308-4242 or (703)305-3014.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Lu, Ph.D., whose telephone number is (571)272-0746. The examiner can normally be reached on Monday-Friday from 9 A.M. to 5 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (571)272-0782.

Any inquiry of a general nature or relating to the status of this application should be directed to the Chemical Matrix receptionist whose telephone number is (703) 308-0196.

Frank Lu
PSA
February 18, 2004

part of the office action

This reactive biotin derivative contains an aminohexanoyl spacer group (termed "X") between biotin and the binding site for proteins, nucleic acids, or other biological molecules. This spacer helps to reduce potential quenching effects of fluorophores attached to the analyte molecule, since biotin binds to "deep" binding sites in avidin or streptavidin. This extra linking arm makes it more accessible for binding, and improves a variety of assays employing biotin-avidin or biotin-streptavidin systems. This amine reactive (succinimidyl ester, SE) derivative can be readily coupled to primary or secondary amines of analyte compounds or proteins under mild conditions. Biotin is a commonly used hapten that can be detected by using it's strong affinity for the proteins avidin (from egg white) or streptavidin. Many avidin or streptavidin conjugates are available that have been fluorescently labeled or are conjugated to an antibody or other detection reagent. This biotin labeling compound has been used in many such detection schemes for peptides, proteins, organelle components, monoclonal antibody analyses, oligonucleotide and microbead labelings. See references below for further information on the use of biotin labeling. See also information contained in our Product **M0785**) page.

References:

- "Oxazolidinones mechanism of action: inhibition of the first peptide bond formation." Patel U, Yan YP, Hobbs FW Jr, Kaczmarczyk J, Slee AM, Pompliano DL, Kurilla MG, Bobkova EV. J Biol Chem 276, 37199-205 (2001)

- "In-situ monitoring of protein labeling reactions by matrix-assisted laser desorption/ionization mass spectrometry." Lu J, Zenobi R. Fresenius J Anal Chem 366, 3-9 (2000)

- "Peptide biotinylation with amine-reactive esters: differential side chain reactivity." Miller BT, Collins TJ, Rogers ME, Kurosky A. Peptides 18, 1585-